REMARKS

Claims 1-27 have been cancelled (non-elected subject matter). Claims 28-57 remain pending. No new matter has been added by virtue of the within amendment, support therefor being found throughout the specification and the original claims of the application.

Applicants appreciate the helpful comments provided by Examiners Harris and Caputa during two telephonic interviews conducted on August 28, 2003 and September 11, 2003, with the undersigned attorney and agent of record. During such interviews, the remaining rejections were discussed in detail, as were possible ways to overcome the rejections. While no definitive agreement was reached, the Examiners indicated that the following would be beneficial in overcoming the enablement rejection: (1) submitting one or more references which would establish a link between the in vitro data provided in the application and in vivo use in the various cell lines; and (2) submission of a Declaration identifying the active component(s) of the active enamel substance, attesting to and describing its effect on the target tissue.

Referring now to the Office Action, claims 28-57 stand rejected under 35 USC §112, first paragraph, for the reasons already made of record. In brief, the position is taken that while the specification is enabling for a method for treating malignant cancer cell lines (such as those listed in Table 1 of the present application), the specification is allegedly non-enabling for a method for preventing or treating malignant or benign neoplasms as presently claimed.

The rejection is traversed.

At the outset, Applicants wish to emphasize that the methods of the invention are limited to treating *epithelially derived and ectodermally derived* benign, semi-malignant or malignant neoplasms which comprises *administering topically* to a mammal in need thereof a therapeutically effective amount of an *active enamel substance*. (See independent claims 28, 48 and 52). It is respectfully submitted that the specification provides ample enabling disclosure

such that the skilled artisan could practice the methods of the invention commensurate in scope with the claims.

For instance, attention is drawn to the present application at page 4, line 35 to page 5, line 31, wherein the topical application of an active enamel substance to a suitable surface at or on affected tissue is clearly described. The application also includes numerous working examples which demonstrate the invention.

Further, Table 1 shows data relative to use of the present invention in ten (10) different cell lines, originating from five (5) different species of tissue (glandular, bone, skin, ovarian and muscle). Each of the cancers exemplified by the cell lines treated and listed in Table 1 are *ectodermally derived*; certain of the cancers which are ectodermally derived also are *epithelially or epidermally derived.* As such, it is respectfully submitted that such data along with the supporting specification provides ample enabling disclosure for the present invention as claimed.

The Office Action goes on to address the unpredictability associated with anti-cancer therapeutics, and references a non-scientific article by Gura (*Science* 278: 1041-1042, 1997). The noted article, nearly six years old, addresses anti-cancer drug screening and seems to indicate that while numerous anti-cancer drugs show promise in cell or animal models, a very limited number of these drugs are successful in human clinical trials.

Applicants submit that the requirements of 35 USC §112, first paragraph, are quite distinct from those of the Food and Drug Administration which will eventually determine whether or not any given drug will enter the therapeutic market.

Attention also is drawn to the *Manual of Patent Examining Procedure*, §2107.03 which reads in part:

> Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to the treatment of human disorders (see *In re Isaacs*, 347 F.2d 889, 146 USPQ 193 (CCPA

> 1963); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974)), even with respect to situations where no art recognized animal models existed for the human disease encompassed by the claims.

Additionally, 35 USC §112 clearly does not require absolute predictability with respect to the practice of every possible embodiment of a claimed invention. For example, in the chemical case of *In re Angstadt,* the CCPA reversed a rejection under Section 112, first paragraph and stated (190 USPQ at 219: bold emphasis added):

> Depriving inventors of claims which adequately protect them and limiting them to claims which practically invite appropriation of the invention while avoiding infringement inevitably has the effect of suppressing disclosure ... Without undue experimentation or effort or expense the combinations which do not work will be readily discovered and, of course, nobody will use them and the claims do not cover them. The dissent wants appellants to make everything predictable n advance, which is impracticable and unreasonable.

Nonetheless, Applicants also submit several published articles which demonstrate that the cell lines employed in the present application indeed are well-established models for testing pharmaceutical compositions and substances in vitro. The references essentially cover three categories: (1) MCF-7 and doxyrubicin in breast cancer; (2) MCF-7 and tamoxifen in breast cancer; and (3) OVCAR-8 and paclitaxel in ovarian cancer. In particular, several abstracts and full copies of the following documents are enclosed: Goldenberg, et al. *Cancer Res*; 42:5147-5151 (1982); Hamilton, et al., *Ann Oncol*; 13:910-918, (2002); Gogas et al., *Ann Oncol.* 13:1737-1742 (2002). The noted articles establish that the in vitro systems used in accordance with the present invention are specific for the disease that they model, and predictive of the outcome in vivo.

Applicants would be pleased to submit the documents in an Information Disclosure Statement should it be necessary for consideration of their relevance.

Applicants also submit a Declaration under 37 CFR §1.132 by inventor Stale Petter Lyngstadaas together with his curriculum vitae and publication listing. In the noted Declaration,

Dr. Lyngstadaas addresses issues related to the active component(s) of the active enamel substance, and details its apoptotic effect on target tissue.

In view of the arguments set forth above, reconsideration and withdrawal of the rejection under 35 USC §112, first paragraph, are thus requested.

Claims 28-57 stand rejected under 35 USC §112, second paragraph, on the grounds that such claims are allegedly rendered vague and indefinite due to the use of several objectionable terms.

While it is noted that a typographical error has been corrected in claim 50, the remaining aspects of the rejection are traversed.

Applicants submit that the noted claims are abundantly clear and definite when read in view of the supporting specification, as is proper.

For example, the Office Action objects to use of the terms "therapeutically effective amount of an active enamel substance" and "enamel matrix derivatives", "derivatives thereof" and "mixtures thereof". "active enamel substance" as those terms appear in the claims. Similarly, the Office Action objects to the term "derivatives", "derivatives thereof" and "mixtures thereof" as they appear in the noted claims.

It is respectfully submitted that such terms are clearly defined in the present application. As such, they would be readily understood by the skilled artisan as clearly defining the metes and bounds of the noted claims.

See, for example, the application at page 1, lines 25-32, where the term "active enamel substance" is defined as a collective term for enamel matrix, enamel matrix derivatives and/or enamel matrix proteins. Additional relevant disclosure concerning these substances is provided beginning at page 5, line 33 to page 10, line 7 of the present application. Particular attention is

directed to page 7, lines 1-8 where examples of proteins suitable for use according to the invention are described.

With respect to the term "therapeutically effective amount of an active enamel substance", attention is directed to the present application at page 19, beginning on line 4, where a detailed discussion of dosages of enamel matrix, enamel matrix derivatives and enamel matrix proteins is provided. While preferred concentrations and dosages are provided, generally speaking, the skilled artisan will appreciate that the term "therapeutically effective amount" corresponds to that amount of the active enamel substance which will provide the desired apoptotic effect.

With respect to the terms "enamel matrix derivatives", "derivatives thereof" and "mixtures thereof" as used in the context of enamel matrix derivates and mixtures, attention is directed to the disclosure at page 7, lines 21-27. That passage clearly describes derivatives and mixtures of the group consisting of enamelins, amelogenins, non-amelogenins, proline-rich non-amelogenins, amelins, tuftelins. Additionally, see in particular, the application at page 7, line 10 where the statement is made that: "In general, the major proteins of an enamel matrix are known as amelogenins. They constitute about 90% w/w of the matrix proteins. The remaining 10% w/w includes proline-rich non-amelogenins, tuftelin, tuft proteins, serum proteins and at least one salivary protein...." A description of other protein substances suitable for use according to the present invention is provided beginning at page 7, line 21.

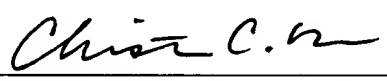
Still further, attention is directed to text beginning at page 7, line 32 which indicates that epithelial cells associated with ameloblasts are believed to be induced to undergo apoptosis by degradation products migrating from the enamel matrix during dental enamel development. The application goes on to state that such degradation products, which generally have a molecular weight between about 3kDa and 25 kDa, such as between 5kDa and 20 kDa, may be particularly effective for use according to the present invention.

In view of such disclosure, it is respectfully submitted that the noted claims would be abundantly clear to those skilled in the art.

Reconsideration and withdrawal of the rejection under 35 USC §112, second paragraph, are requested.

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,



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